Windows to the Ward: Graphically Oriented Report Forms. Presentation of Complex, Interrelated Laboratory Data for Electrophoresis/Immunofixation, Cerebrospinal Fluid, and Urinary Protein Profiles

Background: Automated laboratory analyzers that mass produce data have been linked to information systems for more than two decades, but little progress has been made in developing more comprehensible report forms. Results are still reported in computer-generated printouts containing hundreds of numbers crowded into columns on each printed page.

Methods: We developed three software applications focusing on the graphic presentation of laboratory results.

Results: The first application summarizes data for a patient with a monoclonal gammopathy. The report provides a cumulative graphic presentation of immunofixation/electrophoresis data without any additional interpretation, focuses on a color-coded electrophoresis scan, and records up to 5 years on a single page. The second application deals with cerebrospinal fluid analysis. The report calculates relevant data and graphs the complex relationship between albumin and immunoglobulin results from paired serum and cerebrospinal fluid samples. Manually added interpretive text assures an output comprehensible to clinicians in all specialties. The third application produces a report summarizing quantitatively measured urinary marker protein profiles. The report form is generated by a flexible, completely user-definable knowledge-based system. It calculates numerous ratios and formulae, supports reflex testing, supplies an automated interpretation, and generates a specific graphic signature pattern of the results (MDI LabLink proteinuria differentiation).

Conclusions: Increased clinical demand for graphically oriented report forms 5 years after their introduction has provided evidence that these reports transfer complex laboratory data and results to the clinician more effectively. The highest (more than threefold) increase in demand has been for reports of urinary marker protein profiles that feature a largely self-explanatory graphic signature pattern.

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Instrumentation that can mass produce laboratory test data has been part of clinical chemistry laboratories for more than two decades. Today, performing a test or a test panel has become, in most cases, routine operating procedure. However, little has been accomplished to manage the overload in laboratory data output. The accumulated knowledge that led to the development of new tests is not easily comprehensible to the general medical community. Complex laboratory results are still presented as long lines of numbers and insufficiently flagged as “high” or “low” values. In addition, related results are often scattered on several different sheets of paper. In most cases, interpretation is left to the ordering clinician, making it difficult and time-consuming. Moreover, the clinician is often confronted with laboratory tests outside of his or her expertise.

The past two decades have seen rapid advances in information technology. However, the dominance of computers in business and personal use today is not caused by the phenomenal increase in raw computation power. It has resulted from the replacement of line-based user input with a graphically oriented user interface. Only this graphics-based interface, which presents computer concepts as icons, colors, graphs, and videos, has been able to unlock the power of computers and establish their everyday use outside the informed computer community. In this report, we provide examples to demonstrate that this concept of graphic representation can also help to transfer a large number of interrelated laboratory test results more effectively to the ordering physician, who is often not an expert in the field of reported laboratory values.

Software and Interpretative Software

The following software setup is used routinely at the Kantonsspitale Basel: One computer system covers all areas of laboratory diagnosis: clinical chemistry, coagulation, hematology, hormones, tumor markers, and microbiology (MCS Labordatensysteme, with online access and gateway software from MB Data Control). Reports are color-coded on the right-hand side and presented according to subject on cumulative report sheets.

Interrelated data and advancement of medical knowledge made it necessary to introduce more complex report forms. Some laboratory values, including reference intervals and the results of basic calculations, are transferred to a Novell Network® for further subprocessing with Microsoft Access®. Special report forms without automatic interpretation have been programmed in Microsoft Access in collaboration with the aforementioned companies.

The knowledge-based system “MDI LabLink” was written in Visual Basic® by the authors (1). The best known application of this system is the interpretation of urinary protein profiles. The system requires manual data input. For a limited amount of data, it takes less than 2 min to enter a new sample for an unregistered patient with an unregistered sender and to print out the report form. An interface to laboratory systems, including the
Beckman-Coulter “Datalink (US)/Remisol 2000 (Europe), is currently being tested.

**Graphic Reports**

The introduction of graphic report forms at our institution has led to an increase in the number of tests with interrelated data, but only in cases where the report is largely self-explanatory.

**Cumulative and Graphic Presentation of Laboratory Data Without Additional Interpretation for Immunofixation and Electrophoresis**

The densitometric serum protein electrophoresis scan is a well-established example of graphic presentation of interrelated laboratory data, and physicians are well accustomed to it. In most laboratories, the electrophoresis graph is still presented on a separate, single piece of paper. Today, however, electrophoresis is more likely to be a component in the work-up of patients, e.g., those suspected of having a monoclonal gammopathy, than a single test entity. Large amounts of follow-up data accumulate not only for patients presenting with an established diagnosis of a monoclonal malignancy, but also in cases where results are inconclusive. Therefore, all available data, including electrophoresis, immunofixation results, monoclonal peaks, and immunoglobulin values as well as urine data should be reported on a single page.

With a redesigned graphic report form, all corresponding information can be made visible. In the laboratory, inconclusive or unusual interrelated serum and urine results are detected before the results leave the laboratory, and appropriate action (e.g., additional testing or new sample ordering) can take place immediately. For the sender, all relevant patient information, recent and past, fits on one page, and missing laboratory tests leave a distinct optical gap.

The complete work-up for a patient is also visible when the immunofixation results for serum and urine arrive at different times and/or on different days with separate barcode labels in the laboratory. In most cases, no further text explanation is necessary because all relevant information is, with little training, self-explanatory (Fig. 1). For example, a low urinary creatinine concentration is flagged, and the most likely reason, an incomplete urine collection, is therefore indicated. If further text information is necessary, it is provided mainly as a standardized supplemental legend line commenting on inconclusive samples or on samples with special procedures. This includes the dissolution of immune complex formation with mercaptoethanol and/or the presence of inhomogeneous bands in serum immunofixation.

Finally, the course of a patient’s laboratory data over a larger time span is of special interest. This applies not only to the monitoring of patients presenting with acute infections or rheumatoid disorders or those in posttransplantation monitoring programs, but also to patients with symptoms still lacking a medical diagnosis. Our report form summarizes the laboratory status of a patient and status changes over time for up to five visits. Therefore, changes on a yearly check-up can be compared up to a 5-year time span. The rate of immunofixation orders without clinical necessity, e.g., another immunofixation within 14 days of the first order, remained nearly constant at a rate of 0.7% of total orders (n = 18) in 2000 and 0.8% (n = 24) in 2001.

The report form was introduced in the summer of 1997 and has been used in its current form since the fall of 1999. Five years after its introduction, requests for immunofixation have increased from 1190 to 2125 (78%). For comparison, a detailed look at the request numbers for the years 2000 and 2001 shows the state of current clinical practice in Basel. The number of generated report forms for electrophoreses and immunofixation increased from 2542 to 2753 (8.3%). The number of serum immunofixation reports increased from 1785 to 2125 (19%), whereas requests solely for serum electrophoresis decreased from 757 to 628 (−17%). This has been attributed to the focus on transplantation and stem cell replacement therapy at our institution and the longtime tendency to substitute measurements of single proteins (e.g., C-reactive protein and serum immunoglobulins) for electrophoresis. Sole immunofixation of urine was requested in 3.1% and 3.7% of total orders (a total of 57 requests in 2000 and 71 in 2001). Complete first-time evaluation of patients suspected of a monoclonal gammopathy with concurrent evaluation of urine and serum remained constant at 21% of total orders (392 reports in 2000 and 482 in 2001). The rate of immunofixation orders without clinical necessity (for example, another immunofixation within 14 days of the first order) remained nearly constant at 0.7% of total orders (n = 18) in 2000 and 0.8% (n = 24) in 2001.

**Graphic Presentation, Calculation of Formulas, and Manually Added Comments for Cerebrospinal Fluid**

There are, on the other hand, laboratory examinations that cannot leave the laboratory without an interpretation. Knowledge about the properties of cerebrospinal fluid has evolved rapidly. Correct interpretation requires numerous laboratory results for cerebrospinal fluid and serum values, i.e., cell counts, lactate, glucose, albumin, immunoglobulin profiles, isoelectric focusing, and immunofixation. All relate to each other, and some must be adjusted for age. Immunoglobulin profiles must be plotted on a log/log scale according to the formula developed by Reiber et al. (2–4) to evaluate blood–cerebrospinal fluid barrier function and intrathecal immunoglobulin production (Fig. 2). The one-page cerebrospinal fluid analysis report summarizes all data and classifies and interprets the fundamental pathobiocemical defect. In addition, further microbiological or serologic testing, if appropriate,
This is a cumulative report of a patient with multiple myeloma. At the top are graphs showing serum protein electrophoresis results (dark blue indicates values within the reference interval; light blue indicates decreased concentrations; and red indicates increased concentrations). Below the graphs are the protein electrophoresis data, information on monoclonal proteins, and immunoglobulins (quantitative). Below the protein electrophoresis data are the results for urine, including creatinine, total protein (TP), monoclonal free light chains [Bence Jones protein (BJP); immunofixation result], and free light chains (quantitative). Urinary results are always adjusted to creatinine concentration to maximize the comparability of follow-up examinations. Creatinine-adjusted values reflect changes in the rate of protein excretion more accurately (55–58) and are now part of the guidelines for patients with chronic kidney diseases (59).
Fig. 2. Cerebrospinal fluid analysis report.

Original patient printout containing quantitative and qualitative data for cerebrospinal fluid (CSF) and serum, graphic presentations of specific serum/cerebrospinal fluid ratios (QIgG, QIgA, and QIgM) plotted against the serum/cerebrospinal fluid ratio of albumin (QAlb) on a double logarithmic scale ("Reibergram"), pathobiochemical classification, and examples of typical diseases observed with this constellation. The Reiber scheme has been modified with age-specific reference lines to improve recognition of borderline disturbances (x axis), and the age of the patient is placed prominently above the charts. The reference lines for intrathecal production are additionally plotted in red (y axis). For a detailed explanation of integrated cerebrospinal data reports and a review of disease-related immunoglobulin patterns (IgG, IgA, and IgM with reference to albumin) see Ref. (60). CNS, central nervous system.
is suggested. For the interpretation, only a limited number of text modules seemed necessary at the time the report was designed. Therefore, all interpretations and comments are manually selected text paragraphs. The report is double-checked before it is signed and leaves the laboratory.

The report was introduced by specific request of the neurology department and was regarded initially as an improvement in reporting. The scientific basis is well substantiated, and the graphic presentation provides a “signature pattern”. However, the information provided is not self-explanatory. Only constant education provides the knowledge required to interpret the chart (log albumin to log immunoglobulin as a graphic presentation), and only the additional interpretive text makes the report understandable to clinicians of all specialties. Therefore, clinical acceptance of the design remains limited. Orders before introduction of the report in 1996 totaled 1397, whereas orders in 2001 totaled 1429; this represents a 5-year overall increase of only 2.3%. There are strong yearly fluctuations in the occurrence of neurologic disease that influence the number of orders for the analysis of cerebrospinal fluid. We see, however, a larger clinical demand for cerebrospinal analysis and attribute the 10.1% decrease in the number of cerebrospinal fluid profiles from 2000 (n = 1589) to 2001 (n = 1429) foremost to an overly complicated and incomplete graphic presentation. A more comprehensive approach, including the straightforward graphic presentation of not only cerebrospinal fluid/serum quotient diagrams but also other relevant analytes, such as leukocyte and differential counts, glucose, and lactate, is needed to create a clinically more useful signature pattern.

**GRAPHIC PRESENTATION, CALCULATION OF FORMULAS, AND OBLIGATORY USE OF A KNOWLEDGE-BASED SYSTEM FOR URINARY PROTEIN PROFILES**

The evolution of more specialized fields of medical knowledge has necessitated the use of a genuine knowledge-based system. The general pathobiocchemical classification of renal disease, for example, is fairly straightforward. Interpretation of urinary protein patterns, however, requires the calculation of numerous ratios and formulas. Numerous conditions must be considered when these computed values are transformed into valid interpretations. The presence of postrenal sources of protein that closely resemble glomerular disease must be identified because this situation will impede further interpretation (5, 6). Prerenal causes of proteinuria should be detected by the larger than usual gap between measured total protein and the sum of the main marker proteins. If renal disease is actually present, it should be subclassified into a “selective”, “moderately selective”, or “nonselective” pattern for glomerular disease and the “incomplete” or “complete” form of tubular damage because the patterns give evidence of a patient’s prognosis. In addition, today’s nephelometric detection methods quantify the amount of renal damage (7).

Although it is fairly easy to understand and cross-check a vividly colored report form (Fig. 3), the expert knowledge needed to set up a database for urinary protein analysis is not available in the general laboratory. This was the rationale behind the development of MDI-LabLink. All generated text output of the knowledge-based system is stored in an easily accessible interpretation database, thus enabling full user control over program output [for operation principles and function, see Ref. (1)]. There are now 169 interpretations of specific protein patterns in this database. The large number is not only caused by several complex protein patterns but is also attributable to the additional inclusion of reflex testing in the database. This strategy identifies patterns with less effort and cost because it requires only appropriate measurement of the eligible proteins. Report sheets presented to the clinicians provide a distinct picture of the causative pathobiocchemical defect (Fig. 3). In addition, results of earlier consultations are presented on an additional, cumulative follow-up report in tabular and graphic form [as published for lactate dehydrogenase isoenzymes (1) and urinary proteins (8)]. The follow-up data page further validates the urinary protein profile. Changes must reflect the clinical situation of the patient, or clinicians will quickly doubt the quality of this kind of examination. In 1996, the year proteinuria differentiation was introduced, orders totaled 377. In 2001, five years after its introduction, the total was 1517, an increase of 302.4%, and between the years 2000 and 2001, orders increased 64.4% (n = 923 in 2000). We recently published our long-term experience with this approach of interpreting urinary proteins (7).

**Discussion**

Although >3500 laboratory analytes can be measured routinely, today’s clinicians are expected to order only those tests necessary to diagnose a suspected disease and to keep diagnostic costs to a minimum. However, for the sake of the patient and for liability reasons, laboratory testing should be as complete as possible. This situation has already changed the test request patterns of clinicians and the role of the laboratory within medicine. Increasingly, physicians do not choose a large number of specific tests that the laboratory offers; rather, they request the basic evaluation of a disease or an organ system. The decision for extended analysis depends on the initial test results [hierarchical analysis of samples, dynamic test scheduling, or reflex testing (9, 10)] and takes place in the laboratory. The work-up of hepatitis in most laboratories, for example, is based on basic serology and clinical chemistry results. The results of this extensive analysis, however, must be presented in a form easily understandable by clinicians of all specialties. Surprisingly, although the primary product of the laboratory is actually information, few people have tried to improve or standardize the look of laboratory report sheets. The importance of the
Fig. 3. Proteinuria report form.

Shown are results for a patient with biopsy-confirmed tubular proteinuria, which often remains clinically undetected. Quantitative data of single proteins measurements are presented numerically (left) and graphically (right). Laboratory values referring to the same organ system differ in their units of measurement as well as in their reference intervals. The values are comparable if they are divided by their upper reference (97.5 percentile) limit. The creatinine-adjusted urinary proteins are then ordered according to their molecular weight and plotted against a schematic nephron. Protein concentrations within the reference intervals are plotted as blue bars, increased protein concentrations are plotted as red bars. The proteins now form distinct, instantly recognizable patterns displaying the pathobiochemical lesion. Interpretation of protein patterns produces a pathobiochemical classification and, if appropriate, and desired by the sender, an additional exemplary list of typical diseases observed with this pattern. 

Interpretation

Complete tubular-interstitial with non-selective glomerular proteinuria.

This pattern of urinary proteins is, for example, consistent with:

- primary chronic interstitial renal diseases with secondary glomerular damage, hypertension, nephrosclerosis.

Immunofixation negative; no monoclonal light chains (Bence Jones protein) in urine detected.

If monoclonal gammopathy is suspected, immunofixation in serum recommended.

Legend: Ratio = multiple of upper reference value, class: classification of value
n.d. not done, < conversion below sensitivity, norm normal range, + to **** elevation, >>>> extra elevation

This information is believed to be accurate but is not intended as a substitute for the clinician's independent professional judgement.

Signature: Dr. A. Regeniter

Proteinuria Differentiation Version 3.05
The report form itself appears to have been underemphasized, and Medline has few citations, most of them dating from the 1970s and 1980s (11–13). Aller et al. (14) developed a cytology report to provide an extensive, semiautomated follow-up system. Hewitt et al. (15) reported markedly diverse and potentially confusing test report forms among participating laboratories in a pilot study involving the manageable area of proficiency testing for human immunodeficiency virus. They subsequently developed a general technique to evaluate laboratory report form design (15). In an effort to standardize reporting for cervical cytology results, the Centers for Medicare and Medicaid Services (formerly the Health Care Financing Administration) considered that the use of the 1988 Bethesda system for reporting cervical/vaginal diagnosis in reporting Papanicolaou smear results should be mandatory for all laboratories in the US. A consent reporting statement was formulated in 1993 (16). In the rapidly evolving field of flow cytometry, an exemplary report was proposed with the intention to introduce minimum reporting standards for leukemia and/or lymphoma flow cytometry results (17). It is surprising that no legislative or regulatory action on report standardization has taken place. After all, CLIA’88 was enacted to ensure quality of testing through a combination of mandated minimum quality practices and total quality management (18). Recently, an advisory commission to the President of the United States (19) addressed the issue of reducing error in healthcare, and US Senator Tom Harkin introduced a bill in Congress entitled “Medical Error Reduction Act of 2000” (20).

No financial report dealing with numbers would be complete without a graphic summary of the relevant data. The graphic presentation of laboratory results, in contrast, remains a neglected area, although the computer-assisted approach to serum protein analysis and its graphic presentation was first addressed in the early 1970s (21–23). In 1991, Aller (24) provided many suggestions for improved layout and content of laboratory reports, including the use of PostScript-based laser printers, as well as display workstations and voice response. He stated that:

[Most of the clinical reports have not yet achieved the effectiveness of a report 20+ years ago. . . . The graphical display of the Technicon SMA-12 and it’s descendant the SMAC incorporated graphical displays, so that the clinician could quickly glance at a report and get a good impression of how sick the patient was and (by pattern recognition) see the general category of disease involved.

He concluded that “the next generation of laboratory reports must make better use of the human eye’s capability to rapidly assimilate the mind’s skill at comprehending a picture”. In an approach quite similar to ours, Ritchie (25) created a computer program to interpret serum protein profiles. In addition to the text output, all measured values are converted to centiles; the results are displayed as bar graphs, thus creating a signature pattern. In addition, the effect of age and gender are removed with regard to a similar population, and the wide disparities in mass units are reduced to a common dimension, the length of the bar plot (26). The program is still used daily, and after 17 years of routine operation has been used >250 000 times. In a recent review of the system he concludes that:

[The reluctance to embrace software assistance in laboratory medicine may have serious consequences in the short term and disastrous results within a decade. Expanding the limited algorithm described here to include more traditional chemistry testing could provide the very assistance that all in clinical care desire, a laboratory tool as powerful and adaptable as the traditional physical exam (27).

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![Fig. 4. Patterns of proteinuria.](image-url)

Examples of six different patterns of proteinuria. These graphs constitute the main part of our report form in Fig. 3. Measured proteins in urine include (top to bottom in each graph) α₂-macroglobulin (exclusion of postrenal contamination), IgG, transferrin, albumin (glomerular markers), α₁-microglobulin, and retinol-binding protein (tubular markers). β₂-microglobulin (bottom bar in each graph) is not measured because it has a diagnostic significance similar to that of retinol-binding protein.
This implies that the introduction of complex and interrelated new laboratory analytes requires a straightforward, easy-to-understand graphic presentation, i.e., an easy-to-remember signature pattern (Fig. 4).

In our Medline search, most of the other available literature dealt with the graphic presentation of advanced medical statistics. One interesting approach, however, is a polygon-based graphic representation of laboratory test results by use of nonlinear scaling (28). Quantitative and qualitative but corresponding test results are arranged as equidistant segmented rays that form a circle. The deviation from the basic circle line represents the standardized interpretation. The ray expands outside the normal circle line for a pathologic test result. Depending on the medical results, the figure will form a characteristic, disease-specific pattern (29). The system has been extended with the inclusion of additional clinical information and used successfully on a medical ward (30).

Additional, small alterations to such a graphic report form can account for further substantial differences in perception. Most notably, color seems to play a crucial role in creating an instantly recognizable graphic signature pattern. Verheij et al. (31) have investigated the single effect of adding color to artificial laboratory variables and values. Their addition of color to artificial laboratory tables yielded an approximately sixfold or better improvement in median reaction time in their test participants. Coloring of artificial graphs yielded an improvement in median reaction time of ~2.5-fold or better.

More efforts have been spent on the application of knowledge-based systems to medical problems. Rule-based or knowledge-based systems have been designed for many, but nearly always specific, clinical and laboratory problems (32), including endocrinology (33), diagnosis of hepatitis and lipid disorders (34, 35), test ordering (36), validation of biochemical data (37–40), interpretation of electrophoresis patterns (41), or interpretation of urinary proteins patterns (7, 42). A more comprehensive endeavor has been the development of commercially available computer-based diagnostic systems for general medicine (43–46). Most of these systems have been viewed with skepticism. They produce valid output but are criticized for not being able to differentiate between relevant, less relevant, or even irrelevant information. The output contains diagnoses that a physician would regard as not being particularly helpful in explaining the case or guiding further studies (47). Another approach is the interpretation of data by use of “artificial intelligence” (i.e., neuronal networks). The concept of a computer learning diagnoses by example (48) has also been demonstrated to work for medical data (49) and has successfully contributed to the interpretation of laboratory results (50, 51). Astion and Wilding have published a review (52) of the uses of neuronal networks in pathology and laboratory medicine. Even so, neuronal networks are slow and can handle only a limited amount of input. In the learning phase, on a given day with the same kind of input, the neuronal network might provide a diagnosis completely different from the diagnosis it provided 6 weeks earlier. In addition, neural networks can be overtrained (53). It is difficult to find the point where a network generalizes best and training should stop. The derivation process is hidden in the inner layers, even after learning has been discontinued. There is no explanation for a certain conclusion. Because the pattern might not be obvious, even a sound diagnosis might not be readily accepted. In a recent systematic, detailed review of 173 reports dealing with the use neuronal networks in oncology, Schwarzer et al. observed that:

There is no evidence that artificial networks have provided real progress in the field of diagnosis and prognosis in oncology (54).

The global approach of MDI-LabLink and its urinary protein module combines a vividly colored report sheet with an interpretation database. This concept holds several advantages over a traditional laboratory information system. The first advantage is that the standard Windows® graphic environment makes it easy to use. The second advantage is that rules and text can be tailored with little effort to specific needs and knowledge, allowing the user to maintain complete control over program function and output. This reduces the time needed for tedious interpretation of laboratory values, even if the program output has to be checked for plausibility. Another advantage is that before any program output is generated, built-in algorithms check the plausibility of the entered data and control the work of instrumentation and medical technicians. In addition, a simple transformation makes differently scaled laboratory data comparable and graphable. The graphic display presents the location of the pathobiocchemical defect vividly and quickly provides clinicians with instant understanding of a complex biochemical situation (Fig. 4). Because the information in the graph must correspond to the interpretative text, it also validates that text information. The final advantage is that the follow-up page summarizes, graphs, and interprets all relevant changes in laboratory data. Any relevant change in the urinary protein profile of the patient is evident. This aids in managing the long-term patient, detecting acute complications, evaluating a therapy, and deciding on further clinical action.

Only with the use of tools such as MDI-LabLink, i.e., knowledge-based systems combined with a vivid, graphics-based output presentation, will it be possible to introduce clinicians to new and useful, but unfortunately complex laboratory tests. A specialized cumulative report form, inexpensive to create when compared with the price of a clinical chemistry analyzer, could avoid much confusion, improve patient care, and help reduce overall costs in the healthcare system.

Improved reporting is also a prerequisite for the rapidly evolving field of proteomics. The wealth of information contained in the huge amount of analyzed clusters of
proteins must be presented by visually orientated software. If proteomics challenges traditional methods in clinical chemistry, its results are also going to challenge clinical informatics. Time-pressed clinicians must receive information in the best format for diagnosis and patient care: quickly, reliably, concisely, and intuitively.

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